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Risk Factors for Low Birth Weight: Results From a Case-Control Study in Southern Spain

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ABSTRACT The main objective of this study is to examine the effect of several variables, including altitude of maternal residence, on delivering a low birth weight (LBW) newborn. A case-control study was done. Two hundred forty cases (single newborn weighing less than 2,500 g) and 374 controls (single newborn weighing more than 2,499 g) were included. Information was gathered from the clinical chart of delivering women, through a personal interview and the Spanish Census Bureau (for altitude). Predictors of LBW were assessed through stepwise logistic regression analysis. Several well-known LBW risk factors were identified: hypertension, weight gain during pregnancy, body size (mainly maternal prepregnancy weight), low social class, primiparity, and several conditions (spontaneous delivery, abruptio placentae). Altitude was an independent predictor of LBW at term (more than 37 weeks of gestational age) but not for preterm LBW. Nevertheless, a relationship between altitude and birth weight was not found in controls, although a moderate decreasing gradient with altitude was observed. The limitations of these findings are discussed. Am J Phys Anthropol 105:419–424, 1998.

There are several well-known determinants of low birth weight (LBW), such as hypertension during pregnancy or pre-eclampsia (Arias and Tomich, 1982), weight gain during pregnancy (Seidman et al., 1989; Parker and Abrams, 1992), a previous LBW (Michielutte et al., 1992), and maternal anthropometric measures (height and prepregnancy weight) (Abrams and Newman, 1991). Among the determinants of LBW, altitude has been studied infrequently in developed countries, apart from several reports from Colorado (Beall, 1981; Lichy et al., 1957; Grahn and Kratchman, 1963; McCullough et al., 1977; Weinstein and Haas, 1977; Moore et al., 1986; Yip, 1987; Unger et al., 1988). No report from Europe has been found. This may be due to the fact that many of the countries in which the circumstances of pregnant women are better, and data about them more precise, are relatively low lying (MacFarlane, 1987). We rectify this absence of information by providing data from the province of Granada (southern Spain), which allows the study of the interaction between LBW classic risk factors and other environmental exposures (such as altitude). The second highest mountains of Europe, the Sierra Nevada, are placed within the province' borders. Granada is limited in the south by the Mediterranean sea, thus over a relatively short distance of 50 km, altitude increases from sea level to 3,400 meters.

Our objective is to analyze the determinants of low birth weight, including environ-

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mental exposures, such as the altitude of maternal residence.

METHODS

The study population was selected from women seen at the University of Granada Hospital. This hospital is an 800-bed center with a referral population of 400,000 people. This non-profit institution forms part of the Andalusian Health Service and is the referral center for the coastal area and Sierra Nevada (people usually live below an altitude of 2,500 m). About 30,000 people live at an altitude higher than 1,000 m.

Cases and controls were collected from September 1990 to January 1993. Eligibility criteria for cases were: to deliver a live newborn weighing less than 2,500 g and to live in the referral area of the hospital. A total of 251 cases were identified. In 11 cases, mothers changed their residence during pregnancy, altitude varied, and they were therefore excluded from the present analysis. Of the remaining 240 women, there were 107 who delivered term newborns (gestational age ≥37 weeks) and 133 preterm newborns (gestational age <37 weeks).

To be eligible as a control, mothers should have delivered a single newborn weighing more than 2,499 g. A 5% random sample of all live newborns eligible as controls was drawn. A total of 381 controls were selected. Seven women changed their residence during pregnancy and were excluded, leaving 374 women for the present analysis.

Two physicians (students of the residency program in Preventive Medicine and Public Health at the University of Granada) obtained medical data from hospital and vital records on mother's vital data (age at pregnancy, socioeconomic class, education), obstetric history (parity, previous LBW, abortions), prenatal care (number of visits, date of first visit), conditions during pregnancy (hypertension, anemia, bleeding, diabetes, genitorurinary tract infection), lifestyle (smoking, alcohol), weight gain during pregnancy; and on the newborn (gestational age, weight, height). The altitude of maternal residence was determined by the INE (Spanish Census Bureau). Social class of married women was based on their partner's occupation; in single women, their own job was used. Social class was classified in five levels according to the Black report, from I (highest) to V (lowest level) (Townsend and Davidson, 1982).

Gestational age was calculated as the interval from the first day of the last normal menses to the date of birth. If the day of the last normal menses was missing (in less of 5% of women), the 15th day of that month and/or the ultrasonographic measurement of the fetus, if available, was used.

Prenatal care utilization was measured using the Kessner index (Kessner et al., 1973). This takes into account the month prenatal care began, the number of prenatal visits, and the duration of pregnancy. Three categories of care are delineated for the Kessner index (adequate, intermediate, and inadequate care).

Odds ratios (ORs) and their 95% confidence intervals were computed using the lowest altitude level as reference group. OR is a surrogate for relative risk and, in our study, it indicates the risk of having LBW in one group of women in relation to another group taken as reference. Crude OR estimates and tests for a trend were computed using the StatCalc option of EpiInfo 6 (Dean et al., 1994). To assess the independent predictors for preterm (less than 37 completed weeks) LBW and term LBW forward stepwise unconditional logistic regression was applied (Thompson, 1994). All variables were allowed to be included in the model; however, only those with a $P < 0.1$ were allowed to remain in the final model.

The mean altitude for cases and controls was also computed. These mean were adjusted for several confounders by analysis of covariance. The variables controlled for were the same as those included in logistic regression analysis.

Statistical analyses were performed using the BMDP statistical package, 1990 release (Dixon, 1992).

RESULTS

The main characteristics of the study population are shown in Table 1. Statistical significance differences were found in weight gain during pregnancy (lower in term LBW than in the other groups), level of education (higher in controls), social class (higher in

TABLE 1. Description of the study population

Variable	Low birth weight Term	Low birth weight Preterm	Controls
Maternal age, years (SD)	27.0 (5.3)	27.5 (5.9)	27.8 (5.3)
Weight gain, g/week (SD)	241 (118)	273 (115)	299 (102)*
Body mass index (SD)	23.1 (3.9)	23.9 (4.2)	23.8 (3.6)
Parity (SD)	1.1 (1.5)	1.2 (1.5)	1.1 (1.3)
Hypertension %	17.1	16.3	3.2*
Smoking in pregnancy %	42.0	38.1	31.8
Social class, >III %	16.1	10.8	26.0*
Education level higher than primary school %	29.4	20.8	34.6†
Altitude of maternal residence, meters (SD)	699 (163)	629 (114)	649 (250)*

* $P < 0.001$ (ANOVA).
† $P < 0.05$ (ANOVA).
SD, standard deviation.

controls) and frequency of pregnancy-related hypertension (higher in both preterm and term LBW), and altitude (term LBWs vs. controls). After adjusting for several confounders (socioeconomic class, level of education, previous LBW, prenatal care, parity, weekly weight gain, body mass index, hypertension, and smoking), by analysis of covariance, the difference in altitude among term LBW and controls remained significant ($P = 0.009$).

In Table 2 the relationship between several variables and birth weight in controls is displayed. Altitude did not show a significant association with birth weight ($P = 0.248$); the difference between newborns of mothers with residence at 400 m above sea level or less and those of mothers with residence at 1,000-plus m was 173 g ($P = 0.091$). This difference is similar to those found for smoking and body mass index, although these two latter variables achieved a clear statistical significance. Nevertheless, the birth weight difference between the first and second altitude levels (<400 and 400–699 m) was 139 g, whilst between 400 and 699 m and infants born to mothers living at 1000-plus m it was 44 g.

The results yielded by stepwise logistic regression analyses are given in Tables 3 and 4. The main differences between the predictors for preterm LBW and term LBW apart from the order of entry were: spontaneous delivery, prenatal care (Kessner index) and gestational diabetes were independent risk factors for preterm LBW, whereas altitude of maternal residence and previous LBW increased the risk of term LBW but not preterm LBW risk.

TABLE 2. Factors influencing the birth weight in controls

	Birth weight m ± SEM (g)	*P* value[1]
Altitude (m)		
<400	3517 ± 60	0.248
400–699	3388 ± 50	
700–999	3380 ± 27	
1000+	3344 ± 88	
Body mass index (kg/m^2)		
<19.8	3308 ± 76	0.010
19.8–26	3305 ± 29	
26.1–29	3491 ± 56	
>29	3496 ± 89	
Maternal smoking		
Yes	3320 ± 36	0.014
No	3433 ± 26	
Hypertension		
Yes	3179 ± 199	0.122
No	3361 ± 23	

SEM, standard error of the mean.
[1] Statistical test used was ANOVA.

To further analyze the relationship between altitude and term LBW, the risk of term LBW for different altitudes was adjusted for other well-known predictors of LBW (Table 5). A significant trend was found. However, it should be emphasized that in the highest category (residence at 1,000-plus m) the risk decreased taking as reference lower altitudes (400–699 and 700–999 m); moreover, the frequency of LBW born to mothers living at low altitude (<400 m) was low.

DISCUSSION

The results presented agree in the identification of well-known predictors of LBW: preeclampsia (Arias and Tomich, 1982), weight gain during pregnancy (Seidman et al., 1989; Parker and Abrams, 1992), a previous LBW (Michielutte et al., 1992), prepreg-

TABLE 3. Results of the stepwise logistic regression analysis for preterm low birth weight

Order of entry	Variable	OR (95% CI)
1	Spontaneous delivery	60.76 (22.3–165)
2	Preeclampsia	20.07 (7.12–56.5)
3	Abruptio placentae	85.97 (10.0–739)
4	Social class (ref.: I/II)	
	III	9.99 (3.39–29.5)
	IV/V	3.36 (1.10–10.3)
5	Oligoamnios	8.78 (2.80–27.5)
	Kessner index	
6	(ref.: adequate)	
	Intermediate	2.77 (1.10–7.02)
	Inadequate	7.40 (2.61–21.0)
7	Primiparity	2.27 (1.16–4.43)
8	Weekly weight gain	0.96 (0.92–0.99)
9	Prepregnancy weight	0.82 (0.70–0.96)
10	Diabetes	4.79 (1.20–19.1)
	Constant	0.13 (0.01–1.57)

Hosmer-Lemeshow goodness-of-fit $\chi^2 = 6.56$, $P = 0.584$.

TABLE 4. Results of the stepwise of logistic regression analysis for term low birth weight (LBW)

Order of entry	Variable	OR (95% CI)
1	Preeclampsia	15.18 (5.66–46.8)
2	Weekly weight gain	0.93 (0.90–0.95)
3	Prepregnancy weight	0.72 (0.62–0.85)
4	Oligoamnios	8.71 (2.98–25.5)
5	Altitude	1.16 (1.03–1.31)
6	Social class (ref.: I/II)	
	III	3.03 (1.37–6.69)
	IV/V	1.73 (0.76–3.96)
7	Primiparity	2.30 (1.26–4.20)
8	Previous LBW	3.74 (1.46–9.59)
9	Abruptio placentae	8.55 (0.80–91.9)
	Constant	0.13 (0.01–1.57)

Hosmer-Lemeshow goodness-of-fit $\chi^2 = 4.31$, $P = 0.829$.

nancy weight (Michielutte et al., 1992; Wen et al., 1990), primiparity (Sanjose and Roman, 1991), social class (Wilcox et al., 1995), obstetric conditions such as abruptio placentae or spontaneous delivery (Mavalankar et al., 1992; Michielutte et al., 1992), previous LBW (Wen et al., 1990), prenatal care (Kramer, 1987; Fiscella, 1995), and weight gain during pregnancy (Abrams et al., 1989).

Our results may suggest that altitude is an independent determinant of term LBW. Since the mid-1940s, several studies have reported the association between high altitude and birth weight reduction. All of the studies analyzing the former association have been performed at altitudes much higher than ours (Lichy et al., 1957; Grahn and Kratchman, 1963; McCullough et al., 1977; Yip, 1987; Unger et al., 1988; Notzon et al., 1992; Mazess, 1965; Kruger and Arias-Stella, 1970; Ulstein et al., 1988; Zamudio et al., 1993). Apart from the study by Yip (1987), who controlled for three variables (maternal age, parental education, and marital status), and the study by Notzon et al. (1992), who controlled for maternal education, no other report examining the effect of altitude on birth weight has taken into account other variables affecting birth weight distribution. We have tried to overcome this drawback.

Some human and animal studies have suggested that hypoxia is the main mechanism for birth weight reduction at high altitude (Cotter et al., 1967; Ballew and Haas, 1986; Yancey et al., 1992; Sobrevilla et al., 1971; Mayhew et al., 1991). The oxygen tension and acid-base status of the mother and fetus have been studied indicating that feto-maternal hypoxemia is the hypothesis that better explains the effect of altitude on intrauterine growth retardation. The hypoxia seems a sensible hypothesis for high altitude (>1,500 m) (Yip et al., 1988). Other studies have found anatomic differences in high-altitude placentas (Kruger and Arias-Stella, 1970), low estrogen excretion during pregnancy at high altitude (Sobrevilla et al., 1968) and increase in amniotic fluid index (Yancey and Richards, 1994), but the effect of these factors in birth weight is controversial. The above-mentioned facts and hypotheses suggest that altitude influences birth weight but not gestational age. Our results would agree with this as altitude showed an effect on term LBW and was not an independent predictor of preterm LBW.

Our results on altitude should be interpreted cautiously. First, in controls we could not find a significant relationship between altitude and birth weight, although a certain trend may be appreciated; however, the gradient in the decrease of birth weight was greater at low altitudes than at higher altitudes. Second, the number of cases above 1,000 m is low, thus estimation of risks lacks statistical robustness. Third, the statistical association observed in our data between altitude and LBW may not be due to a higher risk of people living at high altitudes, but due to a lower risk in the population dwelling below 400 m, which was taken as

TABLE 5. Altitude and term LBW: Results from logistic regression analysis

Altitude (meters)	Cases % (n = 110)	Controls % (n = 374)	OR (CI 95%)	CR[b] (CI 95%)
0–399	2.8	10.4	1[a]	1[a]
400–699	59.8	57.8	3.9 (1.1–16.2)	23.6 (2.7–206)
700–999	34.6	27.5	4.7 (1.3–20.2)	32.6 (3.7–286)
>999	2.8	4.3	2.4 (0.3–17.5)	13.7 (1.1–164)
Test for trend			(P = 0.114	P = 0.006

[a] Reference.
[b] Adjusted by socioeconomic class, level of education, previous low birth weight, prenatal care, parity, weight gain per week, body mass index, hypertension, and smoking.

the reference category (the number of term LBW in this group was unusually low). Fourth, selection bias could be another explanation. However, we do not think that selection bias could explain our results. Our hospital is the referral center for the health area lying at high altitude. Selection bias may occur if a higher proportion of normal newborns is delivered in other hospitals and/or at home (due to lack of accesibility), this would not happen with LBW infants as most of them require health care at neonatal unit. We contacted with the provincial office of the Census Bureau to see whether the proportion of women not delivering at hospital changed across different areas. No difference was found. Last, confounding cannot be completely discarded. We have controlled for several known confounders; however, an unmeasured variable related to both altitude and LBW risk may be responsible for the observed association.

In conclusion, the well-known predictors of LBW (hypertension, weight gain, spontaneous delivery, social class, primiparity, etc.) behave in the same manner in our population. Altitude showed an association with LBW at term delivery, although caution should be kept in mind on this association because of the several limitations already commented on. We believe that more research is needed on this subject.

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